

# Drug Interactions and Important Side Effects

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# Disclosure of Financial Relationships

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Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

# Why Drug Interaction Talks Are Painful

## Object Drugs

Amlodipine

Diltiazem

Benazapril

Isradipine

Nicardipine

Nifedipine

Nimodipine

Nisoldipine

Verapamil

Nitrendipine

## Precipitant Drugs

Barbiturates

Carbamazepine

Efavirenz

Oxcarbazepine

Phenytoin

Primidone

Rifabutin

Rifampin

St. John's wort

# Major Absorption Issues

- A 48 yo woman presents for followup. She has a hx of hypothyroidism and has been on L thyroxine for 15 years. She had a TSH checked last week and it was 12. Her last test one year ago was 4. Medical problems include depression, hypertension, GERD and hyperlipidemia. Meds: L thyroxine, Citalopram, Simvastatin, Omeprazole, MVI, and Lisinopril.

What is the most likely cause of the increased TSH?

- A) Omeprazole
- B) Simvastatin
- C) MVI
- D) Citalopram
- E) Lisinopril

# Absorption

## Thyroid hormone/Quinolones

- These drugs are easily bound by cations and binders
  - iron
  - antacids
  - calcium
  - ddl (old formulation)
  - cholestyramine
  - sucralfate
- When a patient has had a stable TSH on thyroid replacement and now has an increase in TSH, absorption problem.

# What Should You Do With A Patient On Thyroxine With A Rising TSH?

- Assess compliance
- Taking FeSo<sub>4</sub>?
- Taking CaCo<sub>3</sub>?
- Taking sucralfate/cholestyramine?
- Taking PPI or H<sub>2</sub> blocker
- Could they have achlorhydria?
- Could the patient have sprue?

- A 44 yo woman with type 2 DM wants to talk about her risk for osteoporosis. Her mother is severely limited by osteoporosis and she wants to prevent this happening to her. She is currently taking Metformin, Rosiglitazone, Omeprazole, HCTZ, Sertraline, and calcium. What medication that she is on is unlikely to increase her risk for osteoporosis?

- A) Rosiglitazone
- B) Omeprazole
- C) Hydrochlorothiazide
- D) Sertraline

# Long Term PPI Use and Risk of Hip Fracture

- Case control study, using 1.8 million patients over age 50 from the British General Practice Research Database (GPRD), with at least one year of followup and no history of hip fracture at database entry.
- 192,000 received at least one prescription for a PPI and 188,000 received at least one prescription for an H2 blocker but no prescription for a PPI. Patients who had used a PPI, or an H2 blocker but no PPI, were matched with up to 10 controls who had received no prescriptions for acid blocking therapy (non-users).

# Long Term PPI Use and Risk of Hip Fracture

- The odds of hip fracture in those using PPI for over a year was 1.44 times that of non-users (95% CI 1.30-1.59).
- A significant dose response effect on hip fracture was seen for PPIs: patients treated with > 1.75 times the usual dose had an OR of 2.65 compared to non-users, while those treated with < 1.75 x the usual dose had an OR of 1.40.
- JAMA 2006; 296: 2947-53.

## Omeprazole Therapy And Reduced Calcium Carbonate Absorption

- Randomized, double-blind, placebo-controlled, crossover trial 18 women randomized to receive omeprazole 20 mg a day or placebo for 7 days. Women received omeprazole or placebo, a MVI and radiolabeled calcium tablets. After a washout period, the patients were crossed over
- Fractional absorption of calcium was reduced from 9.1% on placebo to 3.5% on omeprazole
- Am J Med 2005; 118:778-781

# Problems With PPI's?

- Decreased Ca absorption
- Decreased iron absorption
- Increased hip fracture risk
- Decreased thyroid absorption
- Decreased Ketoconazole/Itraconazole absorption
- Increased risk of C. difficile

# SSRI's Associated With Increased Rate Of Bone Loss

- Study of Osteoporotic fractures was a prospective, cohort study of 2722 community dwelling women. Women were assessed with sequential BMD measurements.
- BMD measurements were made on average 5 years apart
- Mean bone density decreased .47%/yr in women not on a TCA or SSRI, .47%/yr if on a TCA and .82%/yr if on an SSRI
- Arch Intern Med 2007; 167:1240-1245

# Thiazolidinedione Use and Bone Loss in Older Diabetic Adults

- Four year follow-up data from the Health, Aging, and Body Composition observational study.
- Patients age 70-79 with DM, BMD measured at 2 year intervals.
- Six hundred sixty six diabetic patients, 69 reported thiazolidinedione use at annual visit.
- Compared with non TZD users, women patients taking TZD had greater whole body bone loss  $-.61\%/yr$ , lumbar spine  $-.1.23\%/yr$  and trochanter  $-.65\%/yr$
- J Clin Endocrinol Metab 2006; 91:3349- 3354
- Confirmed in Arch Intern Med 2008; 168 (8):820-825.

# Loop Diuretics Bad For The Bones?

- Cohort study of 3,269 men over the age of 65. BMD was measured at baseline and again an average of 4.6 years later
- 84 men were continuous users of loop diuretics, 184 intermittent users and 3004 were non users.
- Annual decline in BMD total hip was  $-.33$  for non users,  $-.58$  for intermittent users and  $-.78$  for continuous users.
- Arch Intern Med 2008; 168 (7): 735-740.

# Drugs Bad For The Bones

- Corticosteroids
- Heparin
- Thiazolidinediones
- SSRI's
- PPI's
- Loop diuretics

# Warfarin Interactions

A 72 y.o. male S/P AVR replacement two years ago for aortic stenosis presents with wide spread bruising on his back/legs and some bruising on the back of both hands. His last INR was three weeks ago and was 3.0. He states he saw an M.D. six days ago for a cough and was put on a medication described as a "white tablet." His chronic medications include: Coumadin 5 mg qd, Albuterol inhaler 2 puffs 4 times a day and Nortryptiline 25 mg qhs.

What medication was he placed on?

- a) Amoxicillin
- b) Codeine
- c) Cefixime
- d) Azithromycin
- e) TMP/Sulfa

# Warfarin Interactions

## Decrease metabolism (increase PT)

### Most Severe

TMP/Sulfa

Erythromycin

Amiodarone

Propafenone

Ketoconazole/fluconazole

Itraconazole

Metronidazole

### Possible\*

Quinolones

Omeprazole

Clarithromycin

Azithromycin

\* Especially in elderly  
and polypharmacy

# Antibiotics and Warfarin

- Retrospective cohort study 104 patients on stable warfarin therapy. Effect on INR of Terazocin (control), Azithromycin (32 patients), Levofloxacin (27) and TMP/Sulfa (16)
- Mean change in INR: Terazocin  $-.15$ , Azithromycin  $+.51$ , Levofloxacin  $+.85$ , TMP/Sulfa  $+1.76$
- Percent patients having a INR  $> 4$ : Terazocin 5%, Azithromycin 31%, Levofloxacin 33%, TMP/Sulfa 69%
- JGIM 2005;20 (7);653-6.

A 39 y.o. woman with a prosthetic aortic valve presents with bruising. Her last INR 6 weeks ago was 2.4, today's INR is 6.5. She has not taken any extra Coumadin. Which of the following when taken on a daily basis could explain her increased INR?

- a) Acetaminophen
- b) Calcium carbonate
- c) OCP
- d) Ranitidine
- e) DOSS

# Warfarin and Acetaminophen

- 2 studies suggest increased INR with Acetaminophen + Warfarin
- > 9100 mg/week led to 10 x risk of having INR > 6\*
- In double blind crossover trial patients on Warfarin + 4 g/d of Acetaminophen had PT 1.75 X control +

\*JAMA 1998;279:657-662

+ Clin Res 1984;32:698a

- A 76 yo man is admitted with increasing SOB. He has a long history of COPD and has had a recent productive cough. He is admitted to the hospital and treated with amoxicillin, prednisone, codeine, and albuterol. PMH: A fib, Hypertension, COPD, GERD. Outpatient meds: Metoprolol, coumadin, pantoprazole, lisinopril. His recent INR 2 weeks ago was 2.2, on hospital day 6 it is 4.3. What is the most likely interaction with coumadin?
- A) Prednisone
- B) Amoxicillin
- C) Codeine
- D) Amoxicillin + Pantoprazole

# Effect of Oral Corticosteroids On Warfarin Therapy

- Retrospective review of patients in ACC who received oral corticosteroids. Patients were excluded if they were treated with any drug with a known interaction with warfarin.
- Mean difference between pre steroid INR and the INR when patients on steroids was 1.24,  $p < .001$ . 62% of the patients had an INR above their targeted range. Mean time to INR elevation was 6.7 days after starting steroids.
- Ann Pharmacother 2006;40:2101-6.

# Herbal Medicines Concern with Warfarin

## Possible Increased anticoagulant effect

Garlic

Ginger

Gingko

Feverfew

Dong Quai

Glucosamine/chondroitin

## Possible Decreased anticoagulant effect

Ginseng

St Johns Wort

# Problems with Statins

- A 60 yo man with CAD and atrial fibrillation comes in for evaluation. He has had severe muscle pain with statin medications. He was initially put on atorvastatin, and then switched to simvastatin when he developed muscle pain. He returns today with continued lower extremity pain. Meds: Simvastatin, Fluoxetine, Omeprazole, Hydrochlorothiazide, Diltiazem, Warfarin. What should you recommend?
  - A) Stop the Diltiazem and begin a B Blocker
  - B) Stop the Simvastatin and begin Lovastatin
  - C) Lower the dose of Simvastatin and add Ezetimibe
  - D) Add NSAIDS for pain control
  - E) Switch to every other day Simvastatin

# Drugs That Increase Risk of Statin Toxicity

- Fibrates (Gemfibrozil >> Fenofibrate)
- Azole antifungals
- Niacin
- Erythromycin/Clarithromycin
- Protease inhibitors
- Verapamil/Diltiazem

# Side Effects of Statins

- Rhabdomyolysis (rare) 3.4/100,000 py
- Hepatotoxicity (rare)
- Liver failure .1-.5/ 100,000 py
- Myalgias 10-15%

# Myalgias And Statins

- Muscle pain or weakness is estimated to occur in 10-15% of patients on statins
- Appears to be dose and possibly drug related
- Check TSH level
- ? Benefit of coenzyme Q10 (low ubiquinone levels?)
- Biopsy of muscle in statin treated patients with myalgia and normal CPK levels have shown myopathy
- Biopsy of muscle in statin treated patients with no symptoms have shown muscle cell damage.

# Coenzyme Q10 for Statin Induced Myalgias

- Double blind placebo controlled trial , all patients taking statin with myalgias
- 32 patients enrolled, 18 received 100mg Coenzyme Q10, 14 received 400 IU of vitamin E (placebo) for 30 days
- Muscle pain and interference with daily activities were assessed before and after treatment
- Pain severity decreased by 40% ( $p < .001$ ), interference with activity decreased by 38% ( $p < .02$ ) in the coenzyme Q10 treated patients, while there was no improvement in pain severity or decrease in interference with activity in the placebo group.
- Am J Card 2007;99 (10):1409-1412.

# Approach To Statin-Related Muscle Symptoms

- Use lowest possible statin dose
- Use lower doses in Asians
- Discontinue medicine and report sudden onset of symptoms
- Holiday off statin before major exertion/surgery
- No need to monitor CK levels in asymptomatic patients(except in patients with drug interaction)
- If myalgias are severe, stop drug ,let symptoms resolve, then start different statin

A 46 yo woman with diabetes and seizure disorder presents with nausea and fatigue. Physical exam is unremarkable. Medications: Glyburide 5mg qd, metformin 850 mg BID, phenytoin 300 mg qd, topiramate 400 mg qd, pantoprazole 40 mg qd. Labs: Na 133 K 3.9 Cl 112 HCO<sub>3</sub> 13 Glu 158 BUN 18 Cr 1.0. What is the most likely cause for this patient's acidosis?

- A) Phenytoin
- B) Topiramate
- C) Metformin
- D) Pantoprazole

# Topiramate And Acidosis

- Topiramate acts as a carbonic anhydrase inhibitor
- Metabolic non anion gap hyperchloremic acidosis can occur
- Average drop in bicarbonate is 4, but can be severe, especially in the setting of surgery

# Use of Alendronate and Risk of Atrial Fibrillation

- Case control study of 719 women with A Fib over 3 years compared to 966 female control subjects with out A Fib.
- More A Fib cases than controls had ever used Alendronate (6.5% vs 4.1%;  $P=.03$ ). Estimated that 3% of A fib in this population due to alendronate use.
- Arch Intern Med 2008; 168 (8):826-831

## But.....

- Population based case-control study, using medical databases from Denmark.
- 3.2% of cases and 2.9% of controls were current users of bisphosphonates for osteoporosis. Etidronate and alendronate were used with almost the same frequency among cases and controls.
- The adjusted relative risk of current use of bisphosphonates compared with non-use was 0.95 (95% confidence interval 0.84 to 1.07).
  - BMJ 2008. 336: 784-785.

A 66 yo woman presents with hypotension and confusion. She was in her usual state of health until 4 hours prior when she felt ill and vomited a small amount of bloody material. She did not seek medical attention for 2 additional hours. She had another episode of emesis this time of a large amount of bloody material. She has also had one episode of maroon stool. PMH- HTN, Osteoporosis and depression. Meds: fluoxetine, benazapril, hydrochlorathiazide, acetaminophen, and estrogen/progestin.

What medication has the the strongest association with UGI bleeding?

- A) Fluoxetine
- B) Benazapril
- C) Hydrochlorathiazide
- D) Acetaminophen
- E) Estrogen

# SSRI'S and GI Bleeding

- Two separate retrospective studies show relative risk for UGI bleeding of 3-4 with the use of SSRI's
- Risk is further increased with concurrent use of a nonsteroidal
- Risk is highest in the elderly
- Strongly consider gastroprotection if combination used in patients with history of UGI bleeding or the elderly
  
- Arch Intern Med 2003;163:59-64
- BMJ 1999; 319 (7217):1106-9.

# Think Before Putting SSRI'S in the Drinking Water

- Probable increased risk of UGI bleed
- Often overlooked cause of hyponatremia
- Sexual dysfunction (20-50%)